CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-409

Chemistry Review(s)

CHEMISTRY REVIEW

NDA 21-409

Singulair™ [ ]

Merck Research Laboratories

Prasad Peri
Division of New Drug Chemistry II
Office of New Drug Chemistry

Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-409

2. REVIEW #: 3

3. REVIEW DATE: 26-July, 2002

4. REVIEWER: Prasad Peri

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	28-September 2001

6. SUBMISSION(S) BEING REVIEWED:

Amendment (BC)	15-July-2002
Amendment (BL)	18-July-2002
Amendment (BC)	22-July-2002
Amendment (BC)	23-July-2002
Amendment (BC)	24-July-2002
Amendment (BC)	25-July-2002
Amendment (BC)	25-July-2002
Amendment (BL)	25-July-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Merck Research Laboratories (Merck & Co., Inc.)

Address: RY 33-720, P. O. Box 2000, Rahway, NJ 07065

Representative: David Altarac, MD, Director, Regulatory Affairs

Telephone: (732) 594 0135

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Singulair™
b) Non-Proprietary Name (USAN): Montelukast Sodium
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Leukotriene Inhibitor

11. DOSAGE FORM: Oral Granules

12. STRENGTH/POTENCY: 4 mg/

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

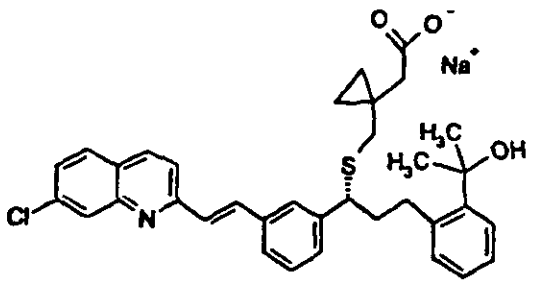
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cyclopropaneacetic acid, 1-((((1R)-1-(3-((1E)-2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)-, monosodium salt

Chemistry Review Data Sheet



$C_{35}H_{35}ClNNaO_3S$
Molecular Weight: 608.18

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
	III			1	Adequate	5/1/02	IR letter sent. See CR 1, page 42
	II			1	Adequate	5/3/02	Page 9
	II			1	Adequate	5/3/02	IR letter sent Page 9 See CR1
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[1] Action codes for DMF Table:
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2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N20829	Merck	DS Info	Approved	N/A	
N20830	Merck	DS Info	Approved	N/A	

18. CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Shelf Life Stability	5/02/02	Draft Complete June 17, 2002	Dr. Guo states that the data supports the applicant's proposal of a ——— shelf life.
EES	DS and DP Sites	10/23/01	Adequate, 4/23/02	All sites acceptable 4/23/02
Pharm/Tox	Proposed levels of ——— in DP	5/1/02	Adequate, Dr. Pei, OND	No safety concerns for the levels of ———
Biopharm	N/A			N/A
LNC	N/A			N/A
Methods Validation	Assay, identity and impurities method was found acceptable by the FDA lab for NDAs 20829 and 20830. Method validation for other attributes will be requested.			Will be sent shortly
OPDRA	Acceptability of the trade Name	2/21/02	Completed, Scott Dallas, ODS	Acceptable with labeling comments passed on to applicant
EA	Exclusion requested	10/23/01		Acceptable
Microbiology	N/A			N/A

The Chemistry Review for NDA 21-409

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval from a CMC standpoint

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

[

]

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The bulk **drug substance** is a white powder and is manufactured and packaged in [redacted]

This site has been inspected and found to have an acceptable GMP status as per EES dated 4/19/02. The intermediates used in the drug substance are obtained from two chemical companies ([redacted]). The DMFs for the intermediates are found adequate.

All the drug substance information (regarding synthesis, manufacture and specifications) have been referenced to the approved NDA 20-829 (Singulair 4 mg and 5 mg chewable tablets).

The drug substance is [redacted]

The **drug product** is white, [redacted] granules packaged in a [redacted] " aluminum foil packet with a [redacted] for ease of opening. The packaged components are child resistant and senior citizen friendly.

The bulk drug product is manufactured by Merck Manufacturing, West Point, PA and is packaged into individual packets at [ ] and is stability tested in Merck Manufacturing Division, Wilson, NC. All drug product manufacturing, packaging and testing facilities have an acceptable EER status.

[ ]

granules at the 10 minute time point.

Merck claims these higher levels [ ] are partly attributed to [ ] during manufacturing and partly due to more than [ ] times. Merck is investigating [ ] options to minimize the effect of [ ] on the drug product during the manufacture. Certificates of analyses for these validation batches manufactured with these controls will be provided to the Agency prior to launch of the drug product in March 2003.

With the recommendation of the Agency, the applicant has tightened the acceptance criteria for oral granules from Q= \ in 20 minutes to Q= \ in 15 minutes.

The commercial batch size is — packets. Stability data for ots (MR 4218- — packets, 1005-46- — packets and 1005-42- — packets) have been provided.

The proposed shelf life for the drug product is — Dr. Ted Guo (Biometrics) in his review states that the sponsor proposed — is supported by the stability data.

- In Chemistry Review 1 the information related the to Drug substance and Drug Product was reviewed. Based on the information provided, comments were sent to the applicant in a fax dated May 7, 2002. The applicant responded to these comments in an amendment dated June 7, 2002.

- In Chemistry Review 2 the responses provided in the amendment dated June 7 were evaluated and list of deficiencies were forwarded to the applicant in a fax dated June 28, 2002. The applicant requested a teleconference with the Agency to clarify issues related to [ ] for

further submission of data by the applicant. This was held on July 10, 2002 at 10:30 AM and the applicant was informed that the dissolution specification for the drug product should be tightened. Following this teleconference, applicant was faxed CMC comments related to the proposed labeling for the packet, carton, PI and PPI.

- The applicant responded to the Agency's fax dated June 28 in an amendment dated July 15, 2002. These responses have been evaluated here, in Chemistry Review 3, along with the responses to the labeling comments provided by the agency on July 12, 2002. Several teleconferences were held between the Agency and the applicant during July 20 2002 and July 25, 2005. Issues related to acceptance criteria for r[ ]

  drug product were discussed. These teleconferences resulted in the applicant revising the [ ] testing to the stability protocol.

B. Description of How the Drug Product is Intended to be Used

The drug product is to be administered orally possibly with food. The approved indication is for patients 12 months to [ ]years and for patients 2 to 5 years who cannot chew tablets.

C. Basis for Approvability or Not-Approval Recommendation

All pending safety and quality issues have been resolved. Issues related to pictures on the complimentary cartons have been forwarded to the division for a divisional perspective and action.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Same date as draft review

Chemistry Team Leader Name/Date

Project Manager Name/Date

C. CC Block

Redacted 32

page(s) of trade secret

and/or confidential

commercial information

(b4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Prasad Peri
7/26/02 12:52:52 PM
CHEMIST
BC Amendments dated 24 July and 25, July 2002
and a BL amendment dated July 25 have
not been linked to this review in DFS
as they were not updated in DFS at
the time of the signoff on DFS. Document
room should close these amendments once AP action is tak

Brian Rogers
7/26/02 01:02:55 PM
CHEMIST
Signed for Guirag Poochikian

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 21-409

2. REVIEW #: 2

3. REVIEW DATE: 27-June, 2002

4. REVIEWER: Prasad Peri

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	28-September 2001

6. SUBMISSION(S) BEING REVIEWED:

Amendment	23-April-2002
Amendment	3-May-2002
Amendment	21-May-2002
Amendment	7-June-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Merck Research Laboratories (Merck & Co., Inc.)

Address: RY 33-720, P. O. Box 2000, Rahway, NJ 07065

Representative: David Altarac, MD, Director, Regulatory Affairs

Telephone: (732) 594 0135

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Singulair™ [redacted]

b) Non-Proprietary Name (USAN): Montelukast Sodium
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Leukotriene Inhibitor

11. DOSAGE FORM: Granules

12. STRENGTH/POTENCY: 4 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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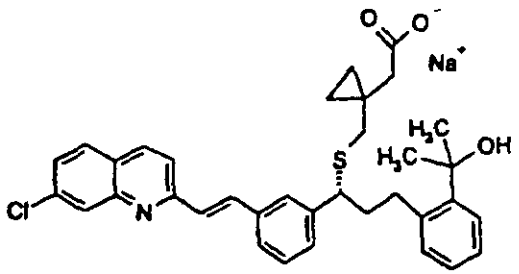
Chemistry Review Data Sheet



$C_{35}H_{35}ClNNaO_3S$
Molecular Weight: 608.18

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

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B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N20829	Merck	DS Info	Approved	N/A	
N20830	Merck	DS Info	Approved	N/A	

18. CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Shelf Life Stability	5/02/02	Draft Complete June 17, 2002	Dr. Guo states that the data supports the applicant's proposal of a ——— shelf life.
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Pharm/Tox	Proposed levels of ——— in DP	5/1/02	Adequate, Dr. Pei, OND	No safety concerns for the levels ———
Biopharm	N/A			N/A
LNC	N/A			N/A
Methods Validation	Assay, identity and impurities method was found acceptable by the FDA lab for NDAs 20829 and 20830. Method validation for other attributes will be requested.			Will be sent shortly
OPDRA	Acceptability of the trade Name	2/21/02	Completed, Scott Dallas, ODS	Acceptable
EA	Exclusion requested	10/23/01		Acceptable
Microbiology	N/A			N/A

The Chemistry Review for NDA 21-409

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable from a CMC standpoint

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None indicated so far

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Chemistry Review 1 found the application approvable and deficiencies were sent to the applicant in a fax dated May 7, 2002. The applicant responded to these comments in an amendments dated May 21, 2002 and June 7, 2002. They are evaluated in this review cycle.

The bulk **drug substance** is a white powder and is manufactured and packaged in

This site has been inspected and found to have an acceptable GMP status as per EES dated 4/19/02. The intermediates used in the drug substance are obtained from two chemical companies The DMFs for the intermediates are found adequate.

All the drug substance information (regarding synthesis, manufacture and specifications) have been referenced to the approved NDA 20-829 (Singulair 4 mg and 5 mg chewable tablets).

The drug substance is

The **drug product** is white, granules packaged in a aluminum foil packet with a for ease of opening. The packaged components are child resistant and senior citizen friendly.

The bulk drug product is manufactured by Merck Manufacturing, West Point, PA and is packaged into individual packets at

and is stability tested in Merck Manufacturing Division, Wilson, NC. All drug product manufacturing, packaging and testing facilities have an acceptable EER status.

[redacted]

The proposed shelf life of the drug product is [redacted] A biometrics consult has been requested (dated 5/2/02) to evaluate the appropriateness of the proposed shelf life based on statistical analysis. Dr. Ted Guo in his draft review states that the sponsor proposed [redacted] is supported by the stability data.

The proposed dissolution and impurities acceptance criteria are not justified based on the data provided. They should be tightened to reflect the data. Comments are being sent to the applicant.

The commercial batch size is [redacted] packets. Stability data for [redacted] lots (MR 4218-[redacted] packets, 1005-46-[redacted] packets and 1005-42-[redacted] packets) have been provided.

B. Description of How the Drug Product is Intended to be Used

The drug product is to be administered orally possibly with food. The proposed indication is for patients [redacted] to 2 years and for patients 2 to [redacted] years who cannot chew tablets.

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable, pending deficiencies listed at the end of the review (pages 50-51).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Same date as draft review
Chemistry Team Leader Name/Date
Project Manager Name/Date

C. CC Block

Redacted 21

page(s) of trade secret and/or confidential commercial information

(b4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Prasad Peri
6/28/02 02:54:08 PM
CHEMIST

Guiragos Poochikian
6/28/02 03:00:54 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

NDA 21-409

Singulair™ [ ]

Merck Research Laboratories

Prasad Peri
Division of New Drug Chemistry II
Office of New Drug Chemistry

Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-409

2. REVIEW #: 1

3. REVIEW DATE: 06-May, 2002

4. REVIEWER: Prasad Peri

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	28-September 2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	28-September-2001

7. NAME & ADDRESS OF APPLICANT:

Name: Merck Research Laboratories (Merck & Co., Inc.)

Address: RY.33-720, P. O. Box 2000, Rahway, NJ 07065

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a) Proprietary Name: Singulair™ ———

b) Non-Proprietary Name (USAN): Montelukast Sodium

c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Leukotriene Inhibitor

11. DOSAGE FORM: Granules

12. STRENGTH/POTENCY: 4 mg

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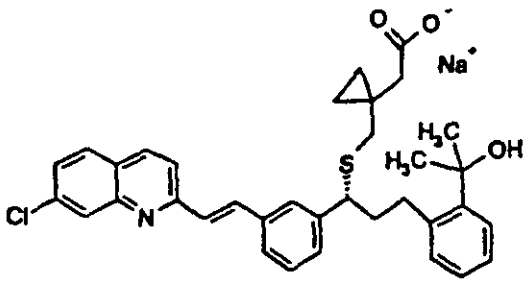

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N20830	Merck	DS Info	Approved	N/A	

Chemistry Review Data Sheet

18. CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Shelf Life Stability	5/02/02	Pending with Dr. Gebert	Dr. Gebert was sent a consult on 5/2/02
EES	DS and DP Sites	10/23/01	Adequate, 4/23/02	All sites acceptable 4/23/02
Pharm/Tox	Proposed levels of ——— in DP	5/1/02	Adequate, Dr. Pei, OND	No safety concerns for the levels of ———
Biopharm	N/A			N/A
LNC	N/A			N/A
Methods Validation	To be sent			Will be sent shortly
OPDRA	Acceptability of the trade Name	2/21/02	Completed, Scott Dallas, ODS	Acceptable
EA	Exclusion requested	10/23/01		Acceptable
Microbiology	N/A			N/A

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 21-409

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable from a CMC standpoint

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The drug substance is

The **drug product** is white, granules packaged in a aluminum foil packet with a for ease of opening. The packaged components are child resistant and senior citizen friendly.

The bulk drug product is manufactured by Merck Manufacturing, West Point, PA and is packaged into individual packets at and is stability tested in Merck Manufacturing Division, Wilson, NC. All drug product manufacturing, packaging and testing facilities have an acceptable EER status.

There are some serious issues with the stability of the drug product when mixed with baby foods like rice, applesauce, etc.

[redacted]

The proposed shelf life of the drug product is [redacted] A biometrics consult has been requested (dated 5/2/02) to evaluate the appropriateness of the proposed shelf life based on statistical analysis.

The proposed dissolution and impurities acceptance criteria are not justified based on the data provided. They should be tightened to reflect the data.

The commercial batch size is [redacted] packets. Stability data for [redacted] lots (MR 4218-[redacted] packets, 1005-46-[redacted] packets and 1005-42-[redacted] packets) have been provided.

B. Description of How the Drug Product is Intended to be Used

The drug product is to be administered orally possibly with food. The proposed indication is for patients [redacted] to 2 years and for patients 2 to [redacted] years who cannot chew tablets.

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable, pending deficiencies listed at the end of the review (pages 50-51).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

Redacted 45

page(s) of trade secret and/or confidential commercial information (b4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Prasad Peri
5/6/02 04:19:35 PM
CHEMIST

Guiragos Poochikian
5/6/02 04:41:44 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL